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Storage Stability Study: is designed to aid data reviewers in their evaluations of the adequacy and appropriateness of storage stability studies (of pesticides and their metabolites that together comprise the total toxic residue in raw and processed commodities). Such studies provide information on the extent of residue decline with the integrity of the residue values reported in experimental samples subjected to storage prior to analysis. The nature and magnitude of the residues in supervised trial samples (raw and processed foods/feeds) are required by 40 CFR 158.240 to support the registration of any pesticide intended for use on a food or feed crop under the amended Federal Insecticide, Fungicide, and Rodenticide Act.

The term "total toxic residue" is used to describe the sum of the parent pesticide and its degradation products, metabolites (free or bound), and impurities that are considered to be of toxicological significance, and therefore warrant regulation.

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HEALTH EFFECTS DIVISION

STANDARD EVALUATION PROCEDURE

STORAGE STABILITY STUDY

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STORAGE STABILITY STUDY

I. INTRODUCTION

A. Purpose of the Standard Evaluation Procedure

This Standard Evaluation Procedure[1/] is designed to aid data reviewers in their evaluations of the adequacy and appropriateness of storage stability studies (of pesticides and their metabolites that together comprise the total toxic residue in raw and processed commodities) that are submitted by petitioners/registrants. Such studies provide information on the extent of residue decline with time under storage conditions, and are needed to validate the integrity of the residue values reported in experimental samples subjected to storage prior to analysis.

The term "total toxic residue" is used to describe the sum of the parent pesticide and its degradation products, metabolites (free or bound), and impurities that are considered to be of toxicological significance, and therefore warrant regulation.

B. Background Information

Data on the nature and magnitude of the residue in supervised trial samples (raw and processed foods/feeds) are required by 40 CFR § 158.240 to support the registration of any pesticide intended for use on a food or feed crop under the amended Federal Insecticide, Fungicide, and Rodenticide Act.

In most cases, samples collected from supervised trials with pesticides undergo a period of storage (usually frozen) prior to their analyses for pesticide residues. During this time it is possible that residue levels in the matrices of interest could change due to catabolism of the pesticide (and/or its metabolites) with storage. Therefore, data need to be provided by the petitioner/registrant to validate the stability of residue levels during such a storage period.

1/ Other topic areas considered in residue chemistry data review [ref. 40 CFR 158.240] are addressed in separate Standard Evaluation Procedure documents.

Data on residue levels in raw and processed foods and feeds are used by the Agency to estimate the exposure of the general population to pesticide residues in food, and for setting and enforcing tolerances for pesticide residues in or on raw and processed foods or feeds under provisions of Sections 408 and 409, respectively, of the Federal Food, Drug, and Cosmetic Act.

Lack of adequate storage stability data has become a major factor in delaying registration of pesticides. The Agency has prepared a position document titled "Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data" 2/ which provides additional background information on the purpose, experimental design and test procedures, and presentation of residue results of a storage stability study.

C. Objective of a Storage Stability Study

A storage stability study should answer the following question: Are the parent pesticide and its metabolite(s) that together comprise the "total toxic residue" to be regulated stable in the matrices of interest during storage?

This information is needed so that the reviewer can determine whether supervised trial residue results truly reflect the level of residue in/on crops at the time of harvest.

(Note: If limited decline of the residue is shown to occur, correction factors should be applied to the field trial residue results to determine the appropriate level at which the proposed tolerance should be established. If extensive decline of the residue is shown to occur, storage of field trial samples prior to analysis should be avoided.)

II. INFORMATION TO BE SUPPLIED

The petitioner/registrant's report on storage stability studies conducted should include all information necessary to provide a complete and accurate description of the commodities (whether raw or processed) that were stored; the test compounds; the experimental design and storage conditions (e.g., temperature,

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2/ Available from the National Technical Information Service.

length of storage, etc.); residue method(s) and instrumentation; storage stability results and reporting of the data; statistical analyses; and, quality control measures/precautions taken to ensure the fidelity of these operations, including the dates for each step above.

Each component expressed in the tolerance is subject to storage stability testing. If the analytical methodology is capable of quantitating each component of the residue individually, then a spiking mixture may be used for fortification purposes. If the analytical methodology is only capable of measuring the total residue, then each component comprising the total toxic residue must be individually tested for storage stability.

A guideline of specific information that should be included in the petitioner/registrant's report of a storage stability study is provided in the Data Reporting Guideline on Storage Stability 3/ that complements this Standard Evaluation Procedure. Related information on Analytical Method(s), the Magnitude of the Residue in Crop Field Trials and in Processed Foods and Feeds are found in the Standard Evaluation Procedures 3/ and Data Reporting Guidelines 3/ on those subject areas.

III. THE DATA EVALUATION PROCESS

A. Prepare A Summary

The initial step in the evaluation process of a storage stability study on a raw agricultural commodity (and, where applicable, processed foods/feeds therefrom) is for the reviewer to carefully examine and summarize the information/data supplied by the petitioner/registrant in his submission to the Agency. Statistical treatments of the data should be independently verified and the quality control precautions noted.

3/ Available from the National Technical Information Service.

B. Identify Data Gaps

Using the Data Reporting Guideline on Storage Stability as a guide (in conjunction with the related Guidelines on Analytical Method(s) and the Magnitude of the Residue in Crop Field Trials and in Processed Foods and Feeds, et al., as appropriate) the reviewer should then look for data gaps--omissions in the information supplied by the petitioner/registrant in his report. These should be duly noted in the reviewer's report, and a judgment made as to which are considered significant enough to adversely affect the review process. Those so identified should be communicated back to the petitioner/registrant by the Product Manager for corrective action.

C. Assess the Appropriateness and Adequacy of the Data

The data reviewer then considers the appropriateness (vis-a-vis the conditions and duration of storage of residue samples from field trial or processing studies, animal feeding or metabolism studies, etc.) and adequacy of the data/information that have been supplied.

The length of time a sample is stored in a storage stability study should reflect the maximum length of time that field trial samples were stored. If field trial samples were stored longer than the storage stability samples, then the field trial sample results may have to be invalidated. The reviewer should also assure that the storage stability samples and field trial samples were stored under similar conditions.

The aforereferenced Data Reporting Guidelines are a useful guide to the various parameters that need to be considered. Appendix 1 of this document discusses specific aspects of those parameters that warrant consideration.

As an adjunct to these, the reviewer should draw upon the technical guidance in the reviewer aids materials that are available, such as the Residue Chemistry Guidelines (aka Subdivision O of the Pesticide Assessment Guidelines). A listing of some suggested source materials is located in Appendix 2 to this document.

Any perceived deficiencies in the data/information supplied should be identified and explained, with a statement as to what steps should be taken to resolve the deficiencies, so that this information can be relayed back to the petitioner/registrant by the Product Manager for appropriate action.

D. Determine the Need for Consultation(s)

In considering the appropriateness and adequacy of the storage stability data that have been supplied, the data reviewer must also determine if consultation(s) with other sources (e.g., another HED Branch) are germane to reaching that decision.

If so, the specific nature of the consultation(s) should be clearly and succinctly stated and directed to the specific parties whose input is sought.

In the interim period until consultation(s) are complete, final judgment on the issue(s) in question should be withheld.

E. Conclude if the Requested Action is Supportable

Lastly, the reviewer considers the results of the storage stability studies and makes a judgment as to whether they support the requested action (tolerance/registration) of the data submitter.

If the data are not supportive, possible alternative action(s) that may be taken by the petitioner/registrant are suggested.

If deficiencies/omissions exist in the submitted data base, the reviewer may have to defer judgment until such time as appropriate corrective action has been rendered by the petitioner/registrant.

(Note: As stated in (D) above, if the outcome of consultation(s) with other sources is still pending, final judgment will need to be held in abeyance pending the outcome of such requests.)

IV. REVIEWER AIDS

There are a large number and variety of source materials that are available to assist the data reviewer in the evaluation process. A listing of some of the more useful references that reside within the Branch is provided in the Reference Section of this document.

APPENDIX 1

MAJOR POINTS TO CONSIDER IN EVALUATING STORAGE STABILITY STUDIES

Include the following:

A. Test Commodities

- What specific plant part(s) [or animal commodities] were subjected to storage stability testing? Were these the same commodities that would ordinarily be shipped in interstate commerce?
- Were the processed commodities (see Pesticide Assessment Guidelines, Table II) from the treated raw agricultural commodity (r.a.c.) subjected to storage stability testing? If not, are such data needed?
- Were aged residue or control samples used in the storage stability testing?
- Were the r.a.c. samples in any way trimmed, cleaned, or otherwise subjected to a means of residue removal in preparation for the storage stability testing? If so, were the recommended procedures of P.A.M. I, §§ 141-2 followed?
- Was any sample compositing or subsampling done in preparation for storage stability testing? If so, were details given? Were the same sample code numbers maintained?
- In what form [whole, chopped, extract, etc.] were the commodities [i.e., matrices of interest] when they were fortified [unless using aged residue samples] and entered into storage? Is the fortification process adequately described?
- For processed commodities, how soon after processing did these commodities enter storage?
- For processed commodities, did transportation/storage conditions approximate normal commercial practices? If not, did this invalidate the samples?

B. The Test Compound(s)

- Is the pesticide and/or its metabolite(s) prone to breakdown? If so, was a storage stability study run in advance of any magnitude of the residue studies to determine adequate storage conditions?

- Were analytical reference grade standards of the parent pesticide and any metabolite(s) of special concern [normally those which, in addition to the parent, comprise the "total toxic residue"] used for fortifications [unless using aged residue samples]? Was the purity of these standards given?
- Is it clear what test compound(s) were used for fortification? For each of the matrices tested?
- If using field-incurred/aged residue samples, what components of the "total toxic residue" were detected at day zero [entry date into storage]?
- Were the fortification ["spiking"] level(s) given for each test compound? For each of the matrices [i.e., raw plant, animal, processed food] tested?
- Is it described how the test compound(s) were prepared for the fortification process [i.e., what solute(s), concentration of the standard solution(s), dilution factors, etc.]?
- If "spiking" with a mixture of test compounds, was testing done to ensure interference would be no problem?

C. <u>The Experimental Design</u>

- Were all the necessary compounds [parent plus metabolite(s) comprising the "total toxic residue"] and matrices of interest tested for storage stability?
- Were the fortification level(s) appropriate? Or, if using aged residue samples, were levels therein of a suitable magnitude?
- Was the duration of the storage stability testing long enough to validate the supervised trial [e.g., crop field trials, animal feeding studies, etc.] and/or processing data of the petition?
- Were there an adequate number of periodic sampling intervals?
- Are zero time [time of fortification or the initial analysis of aged residue samples prior to beginning the storage stability testing] residue values provided?
- Were the storage conditions [temperature, humidity, lighting, container type(s)/size(s), etc.] described, and were they appropriate?
- Are the storage conditions in the stability testing the same as those under which the supervised trial samples awaiting residue analyses were held?
- Was the storage stability study run concurrently with the storage of the supervised trial samples awaiting residue analyses? If not, does this affect the validity of residue levels in the supervised trial samples?

- If appropriate, are the storage conditions identical to standard commerical storage of the commodities (raw and/or processed) from harvest to consumption? If not, are differences sufficiently explained?
- Are all the significant dates given [receipt of samples in the laboratory; sample preparation; sample fortification (unless using aged residue samples); entry into storage; periodic testing; termination of testing; date(s) of residue analysis, including the determinative step].
- Were the supervised trial samples stored in more than one condition (intact; as extracts; etc.)? If so, are there storage stability data to validate each storage condition, and for the appropriate length of time?

D. Residue Method(s) and Instrumentation[4/]

- Was more than one analytical method used in storage stability testing [i.e., did determination of the metabolite(s) require separate method(s)]?
- Were the analytical method(s) adequately identified [e.g., title/designation/date and source]? Are the same method(s) used for residue analysis in the field trial studies?
- Is a complete copy of each analytical method that was used in storage stability testing provided [or available in the over-all data package] with a description of the principles and the stepwise procedure [extraction, clean-up, derivatization, determination, confirmation], and is it clear what chemical species could be determined? Is a non-CBI copy available?
- Is it clear if modifications were made in the analytical procedure(s) and, if so, are they adequately described?
- Was the extraction efficiency of each analytical method(s) demonstrated [especially if dry r.a.c. or processed substrate--or aged residue--samples were used, or if the presence of "bound" residues is suspected?] If dry substrates were used, is the means of rehydration adequately described? If "bound" residues are suspected, were hydrolysis/cleavage procedures and conditions used? Adequately described?
- Were method sensitivity and the limit of detection given? Were they suitably low?

4/ Refer to the Standard Evaluation Procedure on Analytical Method(s) for additional guidance on this subject area.

- Was an internal standard used? If so, was the internal standard identified? Was the internal standard of similar structure, solubility, and stability to the analyte(s) of interest? Have the extraction, clean-up, and determination efficiencies between the analyte(s) of interest and the internal standard demonstrated they are statistically identical throughout the entire analytical procedure? Has the petitioner shown by LC or GC chromatograms that the internal standard and analyte(s) of interest are completely resolved and elute in known windows where no coextractives or other registered pesticides coelute?
- Were any difficulties encountered in the procedure(s) [e.g., emulsions, etc.]? If so, were they adequately described and overcome?
- Were any esoteric reagents/equipment/instrumentation used? If so, can these be substituted for more conventional items without adversely affecting the procedure(s)?
- Are the instrumentation [type, type/specificity of detector(s), column(s) (size, packing materials), carrier gas(es), etc.] and operating parameters [flow rate(s), temperature(s), voltage, etc.] specified? Adequately described?
- How long did it take the analyst to run a sample completely through each analytical procedure, including the determinative step?

E. Storage Stability Results

- Do the results indicate storage stability of the test compound(s) in the test matrices? Is a residue decline indicated?
- If the method(s) measure individual components of the "total toxic residue", do the data show stability of each component? Do the data indicate any interconversions to other component(s) of the "total toxic residue"?
- Are all the raw data reported rather than just average values?
- Were any correction factors [e.g., method recovery, extraction efficiency, field blanks, etc.] applied to the residue values/recovery values reported?
- Are the method(s) of calculating the residue level(s) and percent recovery/ies adequately described [formulae, standard curves, etc.], and illustrated, and the raw data sufficiently detailed so that independent calculations to verify the reported results can be made?
- For volatile pesticides or those prone to breakdown, were the samples analyzed within a few days of collection? If not, are there storage stability data to validate residue levels?

- For samples lacking storage stability data, were samples analyzed within 14 days of collection? If not, are storage stability data needed? Available on a related crop or commodity?
- Are storage stability data for the test compound(s) available on other commodities? If so, how do these residue results compare with other storage stability data for the pesticide? Are any discrepancies explained? Are such data from the same crop group? A closely related crop group? Were conditions of the study similar enough to be useful? Of sufficient duration?
- Do the storage stability data indicate the need for additional information or analyses or another study?

F. Quality Control[5/]

- Are all the raw data reported rather than just the average values?
- What quality assurance measures were taken to ensure the fidelity of the storage stability testing?
- Was the sample/laboratory coding sufficiently clear so that the history of the sample(s) used could be traced?
- Is there any other published or unpublished information on storage stability known to us re this pesticide, r.a.c., or processed commodities/byproducts that must be taken into account?
- Are there Codex/FAO monograph storage stability data available for this r.a.c., its processed commodities/byproducts, or botanically related r.a.c.s treated with this same pesticide? Is so , are such data being used in the evaluation process?
- Are all significant dates given [e.g., date of harvest, date of processing (if applicable), date entering storage, date of extraction, date of analysis, etc.]?
- Were the analyst's worksheets provided? Are they sufficiently detailed?
- Were the person(s) [supervisor, analyst] responsible for the storage stability testing identified [name, title, organization, address, telephone number]?
- Was the storage stability report authenticated (signed) by the responsible personnel?
- Is a contact person for the petitioner/registrant given with title, address, and telephone number?

5/ Refer to the Standard Evaluation Procedure on Analytical Method(s) for additional guidance on this subject area.

- Are the quality control objectives for storage stability stated? If so, are the stated objectives met? If not, does this affect the data generated?
- Were representative chromatograms, spectra, etc., as applicable, provided? Are adequate clean-up and determination [i.e., low background "noise", adequate signal-to-noise ratio, well-defined peaks rather than shoulder bands, etc.] of the test compound(s) indicated?
- Was there replicate testing? If so, were the recovery values reasonably uniform for replicate samples?
- How was sampling done from the stored test samples at the periodic intervals during the storage stability testing to ensure a representative sample was being removed for residue analysis of storage stability?
- Are the calibration procedures for the instrumentation described?
- Were tests performed for interference from storage containers, reagents, plant substrates, plastic labware, etc.?
- If statistical analyses were performed and applied to the results of the storage stability testing, is sufficient information provided to independently validate the results?
- Is there a Registration Standard for this chemical and, if so, is it being used in the evaluation of these data?
- Is a need for a laboratory audit indicated?

REFERENCES

Following is a listing of some of the more useful source materials within the Branch that could prove helpful in reviewing storage stability studies:

(1) Foods and Food Production Encyclopedia, D. M. Considine and G. D. Considine, Van Nostrand Reinhold Company, NY (1982);

(2) F.D.A. Pesticide Analytical Manual, Volumes I and II, available from the National Technical Information Service, Springfield VA (updated periodically);

(3) Official Methods of Analysis of the Association of Official Analytical Chemists, 13th ed., W. Horwitz (editor), Association of Official Analytical Chemists, Washington, D.C. (1980);

(4) Chemistry Laboratory Guidebook, USDA, FSIS, Science, available from the National Technical Information Service, Springfield, VA;

(5) Basic Gas Chromatography, H. M. McNair and E. J. Bonelli, Consolidated Printers, Berkeley, CA (1969);

(6) High Resolution Gas Chromatography, 2d ed., R. R. Freeman, Hewlett Packard Company (1981);

(7) Introduction to Modern Liquid Chromatography, 2d ed., L. R. Snyder and J. J. Kirkland, John Wiley and Sons, Inc., NY (1979);

(8) Various reference texts and journal publications of a scientific or agricultural nature, including FAO/Codex Monographs; Residue Reviews (assorted volumes); Analytical Chemistry (assorted issues); Journal of Agricultural and Food Chemistry (assorted issues); Journal of the Association of Official Analytical Chemists (assorted issues); The Analyst (assorted issues); Journal of High Performance Chromatography (assorted issues);

(9) EPA Analytical Reference Standards and Supplemental Data, available from the National Technical Information Service, Springfield, VA;

(10) FDA Laboratory Information Bulletins, available from the National Technical Information Service, Springfield, VA;

(11) EPA Manual of Analytical Methods for the Analysis of Pesticides in Humans and Environmental Samples, available from the National Technical Information Service, Springfield, VA;

(12) Chemical Separations and Measurements, D. G. Peters, et al., W. B. Saunders Co., Philadelphia, PA (1974);

(13) Statistical Methods Applied to Experiments in Agriculture and Biology, 7th. ed., G. W. Snedecor, Iowa State College Press, Ames, IA (1980);

(14) Statistical Manual of the Association of Official Analytical Chemists, W. J. Youden and E. H. Steiner, Association of Official Analytical Chemists, Arlington, VA (1975);

(15) Basic Statistics: A Primer for the Biomedical Sciences, O. J. Dunn, John Wiley & Sons, Inc., New York, NY (1964);

(16) Subdivision O [Residue Chemistry] of the Pesticide Assessment Guidelines, § 171-3 and § 171-4, prepared by OPTS/EPA, Washington, D.C. (1982);

(17) Code of Federal Regulations [40 CFR 158, 180, 185, and 186], General Services Administration, Washington, D.C., updated annually;

(18) Pesticide Chemical News Guide, R. E. Duggan, editor, Food Chemical News, Inc., Washington, D.C., 1982, updated monthly;

(19) The Pesticide Manual, 7th ed., C. R. Worthing, editor, The British Crop Protection Council, Lavenham Press Limited, Suffolk, England (1983);

(20) "Guidelines on Pesticide Residue Trials to Provide Data for the Registering of Pesticides and the Establishment of Maximum Residue Limits", FAO Plant Protection Bulletin, 29:1/2, pp. 12-27 (1981);

(21) "Guidelines for Data Acquisition and Data Quality Evaluation in Environmental Chemistry", Anal. Chem. 52, 2242-2248 (1980);

(22) Farm Chemicals Handbook, Meister Publishing Co., Willoughby, OH, updated annually;

(23) Chemistry Quality Assurance Handbook, Vols. I and II, USDA, FSIS, Science, available from the National Technical Information Service, Springfield, VA;

(24) Acceptable Common Names and Chemical Names for the Ingredient Statement on Pesticide Labels, 4th ed., C. R. Blalock, et al., editors, OPP/EPA, 1979, available from the National Technical Information Service, Springfield, VA;

(25) Registration Standards on various individual pesticides, prepared by OPTS/EPA, Washington, D.C. (several issued each fiscal year);

(26) Branch files: petition and registration files; reviewer aids; policies; subject files; reading files; et al.;

(27) Effects of Storage (Storage Stability) on Validity of Pesticide Residue, a position document of the EPA, available from the National Technical Information Service, Springfield, VA, NTIS Rpt. No. 540/09-88-002.